UNIVERSITY OF OKLAHOMA MEDICAL CENTER

HEMODYNAMIC AND RESPIRATORY EFFECTS OF DOPAMINE ON SEPTIC SHOCK IN THE MONKEY

Clarence A. Guenter and Lerner B. Hinshaw

Technical Report No. 27
University of Oklahoma Medical Center THEMIS Contract

MEDICAL CENTER RESEARCH AND DEVELOPMENT OFFICE
OF THE UNIVERSITY OF OKLAHOMA FOUNDATION, INC.
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ABSTRACT

This study explored the responses of the rhesus monkey in endotoxin or septic shock, to dopamine (3-hydroxytyramine) and documents metabolic and respiratory effects of maintaining the cardiac output above control levels in those animals. A decrease in cardiac output and systemic arterial pressure occurred in all animals following infusion of endotoxin. Seven were then studied during increasing infusion rates of dopamine (0.5 to 10.0 mg/min) and 5 animals received similar volumes of saline. Each increment in dopamine dose resulted in increased cardiac output. Heart rate, right atrial pressure, and systemic pressure were not altered significantly, but the systemic resistance decreased with each increment in dopamine administered. Two animals in shock after administration of live *E. coli* organisms had a similar response to dopamine. These parameters were unchanged in the animals that received saline, except at the highest infusion rates.

In five animals the cardiac output was raised from 107 to 213 ml/kg/min by a constant infusion of 1.0 to 1.5 mg/min of dopamine. Maintenance of the cardiac output above pre-shock levels did not reverse the metabolic acidosis, hyperventilation or increased alveoloarterial oxygen gradients which occurred during the shock period prior to the dopamine infusion.

INTRODUCTION

Complex illnesses involving multiple organ systems frequently prevent interpretation of pathophysiology documented in patients in shock. Thus, the use of an animal model provides distinct advantages in exploring mechanisms and defining responses to therapy. As reviewed recently (8), the primate has potential advantages over other animal species as a shock model. Shock due to administration of endotoxin or live organisms (*E. coli*) in the rhesus monkey is associated with decreased peripheral resistance, decreased or increased cardiac output and low or normal right atrial pressure (8,11,18), thus simulating the shock observed in many patients (10,17,24). Decreased venous return is an important mechanism of decreased cardiac output and systemic pressure, following the administration of endotoxin in the dog (23). Lansing and Hinshaw demonstrated that pre-treatment with dopamine (3-hydroxy-tyramine) partially prevented the decrease in venous return in dogs (14). In two recent clinical studies (15,21) the cardiac output increased, and peripheral resistance decreased during the infusion of dopamine in several patients with septic shock. The increased cardiac output, increased venous return and decreased peripheral resistance make dopamine particularly promising as an agent to improve tissue perfusion in this form of shock. Several studies have described the effects of dopamine on regional circulation, however, no systematic analysis of the response of the subhuman primate in shock to dopamine infusion has been reported.

This study documents dopamine dose-response relationships in the rhesus monkey in endotoxin and septic shock, and explores the effect of hemodynamic

improvement during constant infusion of dopamine, on metabolic and respiratory abnormalities characteristic of the animals in shock.

METHODS

Fourteen rhesus monkeys of both sexes, ranging in weight from 4.7 to 8.2 kgs, were selected for this study. The animals were captured in the wild and used after appropriate inspection to exclude transmissible disease. All were in apparent good health. In each instance the animal was given 20 to 30 mg/kg of sodium pentobarbital intravenously. Supplemental intravenous pentobarbital was administered occasionally when the animal showed evidence of rousing. The animal was placed in the supine position, and the femoral artery and vein were isolated. A No. 6 NIH woven nylon catheter was advanced to the right atrium under fluoroscopic control and a teflon needle introduced into the femoral artery. A cuffed endotracheal tube was introduced into the upper trachea and the cuff inflated to permit collection of expired gases. The endotracheal tube was connected to a breathing valve with an 8 ml dead space, and expired gases were collected in a water-sealed spirometer during at least a two minute period. Simultaneous determinations of arterial PCO_2, PO_2 and pH were performed.

The expired gases and arterial blood were analyzed on an Instrumentation Laboratories blood gas analyzer and pH electrode. Plasma bicarbonate was calculated from the Siggaard-Andersen nomogram (19). Minute ventilation, tidal volume, oxygen consumption, carbon dioxide production, respiratory exchange ratio, physiological dead space, and alveolar PO_2 were calculated using this data (6). Alveolar PCO_2 was assumed equal to arterial PCO_2.

The cardiac output was measured during the expired gas collection by the indicator dilution technique. Indocyanine green (1.0 mg) was injected into the right atrium with sampling from the femoral artery. The blood was withdrawn by a Harvard infusion pump at the rate of 23 ml/min through a Gilford densitometer cuvette and the blood was reinfused. The volume withdrawn during each dye curve was less than 20 ml and was associated with a mean systemic pressure drop of less than 10 mm Hg. The area under the curve was determined by the semilogarithmic plotting technique or a Gilford model 104 Dye Curve Computer. At least duplicate determinations were made in each instance. Pressures were recorded from catheters in the right atrium and femoral artery by means of Statham P23 Db pressure transducers. A Sanborn 350 Series ultraviolet photographic recorder was employed.

Baseline hemodynamic, ventilatory and arterial blood analyses were performed. Twelve animals were then given intravenous infusions of 4 mg/kg of *E. coli* endotoxin (Difco) over a 3 to 5 minute period. Two animals were given 4 to 8 x 10^9 organisms per kg of live *E. coli*, prepared as previously described (12). The studies were repeated when the systemic arterial pressure decreased at least 30 mm Hg from control values. Following the assessment in the hypotensive period, infusion of dopamine[1] was begun in seven animals of the endotoxin group, and both of the *E. coli* animals. A dose response curve was carried out at infusion rates of 0.5, 1.0, 1.5, 2.0, 5.0 and 10.0 mg dopamine per minute[2]. The dopamine was reconstituted in a saline solution in a concentration of 1.0 mg/ml and infused by a Holter infusion pump. Five control animals received similar volumes of isotonic

saline. At least 5 minutes of infusion proceeded the hemodynamic measurements at each successive dose level. Following the performance of the dose response curve, 5 of these animals in the endotoxin group were given a constant infusion of 1.0 to 1.5 ml/min of the dopamine solution (1-1.5 mg/min) for 60 minutes and the 5 control animals received 1.5 ml/min of saline. Measurements were performed at 5 minutes, 30 minutes, and 60 minutes of infusion. The data was analyzed by the t test.

RESULTS

All animals given endotoxin or live *E. coli* organisms developed severe hypotension which was associated with a decreased cardiac output.

Hemodynamic Response to Increasing Doses of Dopamine

Figure 1 illustrates the changes in cardiac output observed during infusion of dopamine and saline 0 - 2.0 ml/min into animals in shock. The increase in cardiac output was significant ($p<.05$) at each increment in dopamine dose and did not occur in the animals given saline only. Since there was no significant increase in heart rate, the increase in cardiac output was due to increased stroke volume. At doses of 5 and 10 ml/minute, the cardiac output increased in the saline and the dopamine treated animals. The right atrial pressure did not change significantly up to 2.0 mg/minute but increased at higher infusion rates in both the dopamine and saline treated animals, perhaps related to the volume of infusion.

The mean systemic pressure demonstrated no significant change over the entire dose range. Thus, systemic vascular resistance (Figure 2) decreased progressively with each increment in dopamine dose, but was unaltered in the animals receiving saline. Changes in systemic resistance were significantly

different from the pre-drug shock value at all doses greater than 1.0 mg/min ($p<.05$). No arrhythmias occurred throughout the dose range evaluated.

The mean values for the two animals given live *E. coli* are listed in Table 1. The cardiac output increased with each increment in dopamine dose. Heart rate did not change significantly, systemic pressure increased minimally at the highest dopamine dosage, systemic resistance decreased progressively with increased dopamine infusion, and right atrial pressure did not rise except at infusion rates of 5 and 10 ml/min. These changes are all similar to those seen in the animals given endotoxin.

Effects of Constant Infusion of Dopamine

Table 2 lists the hemodynamic characteristics of the animals before endotoxin, in shock, and during the continuous infusion in the group of animals receiving dopamine or saline. During the control period, the mean initial cardiac output was lower in the saline than the dopamine group, but this difference was not significant. The cardiac output decreased in both groups during shock. During the continuous infusion, the mean cardiac output was maintained above control levels in the dopamine group, but remained below control levels in the saline group. The hypotension which developed in both groups was sustained during the infusion of dopamine or saline. The mean systemic resistance was decreased during the shock period in both groups, and decreased significantly in the dopamine group during the continuous infusion. Although the heart rate increased during the shock period in both groups, the mean values were unchanged during dopamine infusion and decreased during saline infusion, so that the values during the constant infusion were significantly different ($p<.05$).

The metabolic, ventilatory and blood gas exchange data for animals receiving saline and dopamine infusions are listed in Table 3. Oxygen consumption was similar in the two groups during the initial control period and during shock. The mean oxygen consumption increased during the dopamine infusion, and although the change in oxygen consumption did not reach levels of statistical significance, the difference between saline and dopamine groups was significant ($p<.05$). Minute ventilation increased in both groups during shock, and continued to increase during the infusion of dopamine, but demonstrated no change during the infusion of saline. The mean arterial PO_2 decreased during the shock period in both groups, and remained low during the continuous infusion. Since all the animals were hyperventilating, the defect in oxygen transport is better illustrated by the calculated alveolo-arterial (A-a) gradient. The mean A-a gradient increased during shock in both groups and remained elevated during the infusion of saline or dopamine. As suggested by the increase in minute ventilation, the arterial PCO_2 decreased during shock and remained low throughout the study. The mean pH decreased in both groups throughout the study, suggesting a metabolic acidosis; this is further reflected by the decrease in calculated bicarbonate. The initial, pre-shock bicarbonate values were significantly different in the 2 groups for reasons which are not apparent, but the values were more nearly comparable during the shock period.

DISCUSSION

Before treatment, the monkeys in this study developed the hemodynamic changes previously described in endotoxin or *E. coli* induced shock (8). These include a sustained decrease in cardiac output and mean arterial pressure, metabolic acidosis, hyperventilation, and increased alveolo-arterial oxygen gradients.

Interest in correcting the hemodynamic derangement in endotoxin or septic shock has prompted the use of numerous agents. Isoproterenol has reversed the hemodynamic and pulmonary alterations in sheep (9), and improved the hemodynamic status and survival rate of the dog (20). Studies in patients (13,16,21) also suggested salutary effects of isoproterenol infusion. Anderson, James, Bredenberg and Hardaway (2) reported patients in septic shock treated with phenoxybenzamine and observed substantial clinical and hemodynamic improvement. Similar results have been obtained in endotoxin shock in the rhesus monkey (22). Recently, the hemodynamic responses to dopamine have been documented in several studies. Dogs in hemorrhagic shock (5) increased their systemic pressure and cardiac output during the infusion of dopamine. Renal and coronary blood flow was increased but peripheral resistance was unchanged. Several patients with severe hypotension (15,21) demonstrated increased cardiac output, decreased peripheral resistance and increased urine output, during dopamine infusion. Furthermore, ventricular arrhythmias were less troublesome in some patients given dopamine, than during isoproterenol infusion (15). This may be related to the improvement in coronary blood flow which has been demonstrated with dopamine infusion (4,5).

In this study we have defined the hemodynamic response of the rhesus monkey in septic shock to dopamine infusion. The increase in cardiac output and decrease in systemic vascular resistance observed with dopamine was not observed in the animals given saline infusions, or in twelve animals previously studied in this manner (8). Elevated right atrial pressures observed at doses of 5 and 10 mg/minute (1-2.5 mg/kg/min) were probably related to the volume of fluid infused since saline infusion resulted in

similar elevations of pressure. Since the systemic resistance uniformly decreased during the infusion of dopamine, the alpha adrenergic effects emphasized in the dog (7) may be of less significance in this preparation. Furthermore, the dose required to produce hemodynamic effects in these studies is more than 10 times as great on a body weight basis, than that previously reported in dogs (5) or humans (21). Even at the very high dose of 2.0 mg/kg/minute, no vasoconstrictor effect was obtained. This may reflect a species difference in the rhesus monkey.

Metabolic acidosis associated with lactic acid accumulation has been previously demonstrated in the monkey (8), and is commonly recognized clinically. Whether this occurs as a result of poor tissue perfusion or a primary cellular effect of endotoxin has not been established. Bell and Schloerb (3) assessed extracellular and intracellular hydrogen ion changes in dogs with comparable degrees of hypotension due to hemorrhage and endotoxin. The endotoxin group developed a much more severe intracellular acidosis. Although this might be explained by different effective tissue perfusion in the groups of hypotensive animals, tissue toxicity was not excluded. Anas, Neely and Hardy (1) documented a dramatic decrease in oxygen consumption in dogs in endotoxin shock. This impaired oxygen uptake did not closely parallel the cardiac output, although it was improved when the cardiac output was increased by fluid administration. Starzecki and Spink (20) restored the cardiac index in dogs with endotoxin shock to greater than pre-shock levels, by infusing isoproterenol, but the lactic acid levels and acidosis persisted for several hours. Thus the precise interrelationship of oxygen consumption, tissue perfusion, cardiac output and metabolic acidosis

is not defined. In our animals, the oxygen consumption during shock was not altered significantly from the control period. Although the mean oxygen consumption increased with the dopamine infusion, this was not statistically significant. Since the metabolic acidosis was not decreased even though cardiac output was increased during dopamine infusion, it is possible that effective tissue perfusion was not increased. On the other hand, this may support evidence reviewed by Zweifach and Janoff (25), suggesting primary cellular metabolic effects of endotoxin unrelated to tissue perfusion.

Improvement in cardiac output during dopamine infusion did not improve pulmonary blood gas exchange as indicated by the alveolo-arterial oxygen tension gradients. Since the oxygen content of venous blood was not measured, the degree of intrapulmonary shunt was not calculated. The increase in cardiac output in response to dopamine would probably increase the venous oxygen content, thus one would predict a decrease in A-a gradient. This did not occur, suggesting that the intrapulmonary shunt was actually increased despite improved cardiac output.

The possibility that hemodynamic effects and tissue perfusion in response to a drug may be related to stage of shock must be entertained. The time of drug administration in this study was selected on the basis of significant hypotension. Respiratory and metabolic changes were thus well established. Earlier institution of dopamine infusion, or higher doses of continuous infusion were not evaluated.

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Table 1. Hemodynamic responses to increasing doses of Dopamine. Mean values of two animals in shock following infusion of *E. coli* organisms.

	Shock	Dopamine Infusion (mg/min)			
		1.0	2.0	5.0	10.0
Cardiac Output (ml/kg/min)	161	211	228	275	336
Heart Rate (per min)	207	220	219	220	209
Systemic Pressure (mm Hg)	65	52	62	67	73
Systemic Resistance (dynes-sec-cm^5)	6740	3990	4154	3696	3340
Right Atrial Pressure (mm Hg)	1.2	1.7	1.9	2.5	3.6

Table 2. Hemodynamic characteristics of animals prior to endotoxin, in shock, and during infusion of dopamine or saline

			Control	Shock	Dopamine Infusion		
					5 min	30 min	60 min
Cardiac Output (ml/kg/min)	D	Mean	174	107	213*	206*	180
		SE	(18)	(7)	(10)	(26)	(8)
	S	Mean	140	98	130	124	130
		SE	(22)	(29)	(27)	(26)	(26)
Systemic Pressure (mm Hg)	D	Mean	128	61	59	57	61
		SE	(6.3)	(5.8)	(2.8)	(4.2)	(4.6)
	S	Mean	113	57	59	68	73
		SE	(2.8)	(11.6)	(8.0)	(17.1)	(18.0)
Systemic Resistance (dynes-sec-cm^5)	D	Mean	8620	6640	3150*	3350*	4020*
		SE	(703)	(870)	(218)	(784)	(551)
	S	Mean	11720	7015	6725	8170	8525
		SE	(1400)	(3040)	(2000)	(2350)	(2450)
Heart Rate (per min)	D	Mean	192	206	209*	204*	207*
		SE	(8)	(15)	(11)	(12)	(11)
	S	Mean	155	185	168	168	169
		SE	(16)	(17)	(11)	(9)	(7)

D = values for 5 animals receiving dopamine
S = values for 5 animals receiving saline
* indicates mean values significantly different ($p<.05$) from saline controls

Table 3. Ventilation and blood gas exchange prior to endotoxin, in shock, and during infusion of dopamine or saline

			Control	Shock	Dopamine Infusion		
					5 min	30 min	60 min
Oxygen Consumption (ml/kg/min)	D	Mean	7.6	7.3	9.6	9.8*	10.1*
		SE	(0.6)	(0.8)	(0.7)	(0.6)	(0.8)
	S	Mean	6.3	6.5	7.1	6.0	7.3
		SE	(1.6)	(1.9)	(1.7)	(0.9)	(0.7)
Minute Ventilation (ml/kg/min)	D	Mean	216	260	314	357	343
		SE	(16)	(25)	(26)	(26)	(53)
	S	Mean	196	277	259	260	283
		SE	(42)	(67)	(45)	(42)	(22)
PaO_2 (mm Hg)	D	Mean	76	71	74	73	75
		SE	(3.6)	(6.4)	(5.8)	(8.3)	(7.4)
	S	Mean	89	64	69	73	67
		SE	(5.6)	(6.7)	(10.0)	(10.0)	(8.2)
Alveolo-Arterial Oxygen Gradients (mm Hg)	D	Mean	7	26	16	25	25
		SE	(2.7)	(8.9)	(7.9)	(9)	(12)
	S	Mean	9.0	40	25	34	30
		SE	(4.5)	(6.7)	(10.0)	(12.5)	(11.0)

Table 3. (cont) Ventilation and blood gas exchange prior to endotoxin, in shock, and during infusion of dopamine or saline

			Control	Shock	Dopamine Infusion		
					5 min	30 min	60 min
Pa CO_2 (mm Hg)	D	Mean	45	34	38	35	34
		SE	(1.4)	(1.9)	(2.3)	(3.7)	(3.7)
	S	Mean	40	35	35	36	37
		SE	(5.8)	(2.9)	(3.2)	(2.5)	(2.2)
pH (units)	D	Mean	7.44	7.42	7.32	7.34	7.35
		SE	(0.02)	(0.02)	(0.03)	(0.04)	(0.02)
	S	Mean	7.38	7.38	7.34	7.34	7.32
		SE	(0.02)	(0.02)	(0.02)	(0.01)	(0.02)
HCO_3 (meq/ℓ)	D	Mean	30.0*	22.0	18.9	18.0	17.6
		SE	(0.9)	(0.7)	(0.5)	(1.1)	(1.3)
	S	Mean	23.0	19.8	18.5	18.5	19.0
		SE	(1.1)	(1.1)	(1.6)	(1.6)	(1.4)

D = values for 5 animals receiving dopamine
S = values for 5 animals receiving saline
* indicates values significantly different ($p<.05$) from saline controls

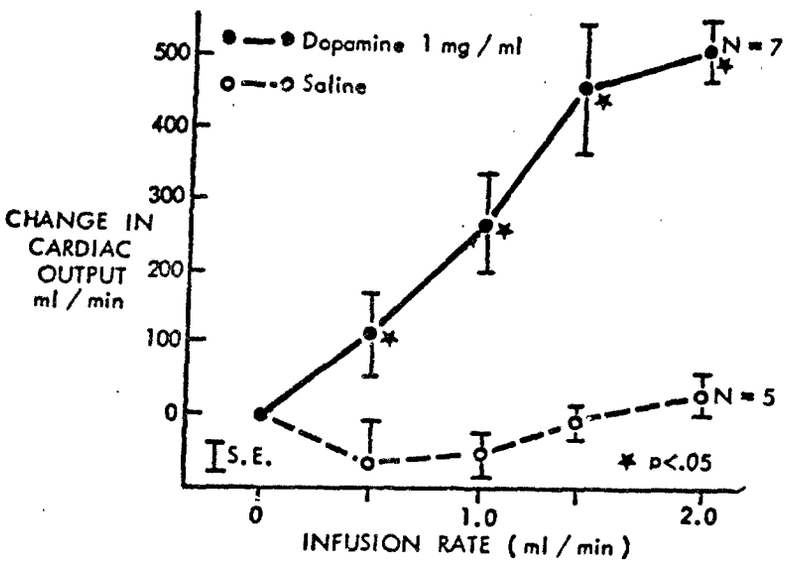

Figure 1. Change in cardiac output in response to dopamine infusion compared to equal volumes of saline.

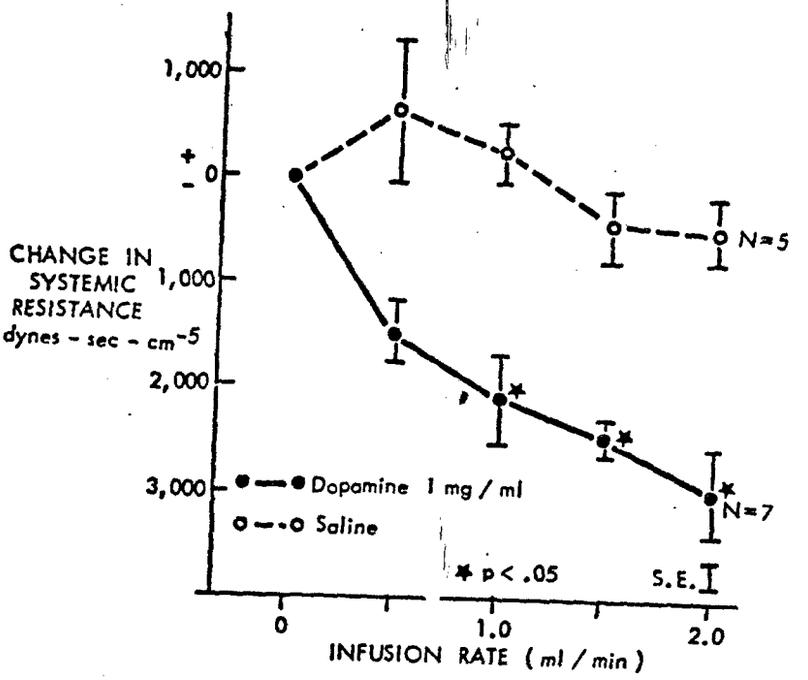

Figure 2. Change in systemic resistance in response to dopamine infusion compared to equal volumes of saline.

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13. ABSTRACT

This study explored the responses of the rhesus monkey in endotoxin or septic shock, to dopamine (3-hydroxytyramine) and documents metabolic and respiratory effects of maintaining the cardiac output above control levels in those animals. A decrease in cardiac output and systemic arterial pressure occurred in all animals following infusion of endotoxin. Seven were then studied during increasing infusion rates of dopamine (0.5 to 10.0 mg/min) and 5 animals received similar volumes of saline. Each increment in dopamine dose resulted in increased cardiac output. Heart rate, right atrial pressure, and systemic pressure were not altered significantly, but the systemic resistance decreased with each increment in dopamine administered. Two animals in shock after administration of live E. coli organisms had a similar response to dopamine. These parameters were unchanged in the animals that received saline, except at the highest infusion rates.

In five animals the cardiac output was raised from 107 to 213 ml/kg/min by a constant infusion of 1.0 to 1.5 mg/min of dopamine. Maintenance of the cardiac output above pre-shock levels did not reverse the metabolic acidosis, hyperventilation or increased alveoloarterial oxygen gradients which occurred during the shock period prior to the dopamine infusion.

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